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(21) International Application Number: PCT/EP95/03522 (22) International Filing Date: 7 September 1995 (07.09.95) (30) Priority Data: 9418092.4                      8 September 1994 (08.09.94)    GB (71) Applicant (for all designated States except US): RED CROSS FOUNDATION CENTRAL LABORATORY BLOOD TRANSFUSION SERVICE SRC [CH/CH], Wankdorfstrasse 10, CH-3000 Bern 22 (CH). (72) Inventors; and (75) Inventors/Applicants (for US only): BRUEGGER, René [CH/CH]; Luternauweg 2, CH-3006 Berne (CH). GEN- NARI, Katharina [CH/CH]; Alpenstrasse 18, CH-3045 Meikirch (CH). HODLER, Gerhard [CH/CH]; Farbstrasse 11, CH-3076 Worb (CH). WUEST, Bernard [CH/CH]; Chemin de la Redoute 6, CH-1752 Villars-sur-Glâne (CH). (74) Agent: GRUBB, Philip, W.; Sandoz Technology Ltd., Patent & Trademark Div., Lichtstrasse 35, CH-4002 Basle (CH).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).  <b>Published</b> <i>With international search report.            Before the expiration of the time limit for amending the            claims and to be republished in the event of the receipt of            amendments.</i>	
(54) Title: LIQUID IMMUNOGLOBULIN FORMULATIONS			
(57) Abstract			
Immunoglobulin preparations, particularly liquid preparations of immunoglobulin G for intravenous infusion, are stabilized against dimer formation by the addition of one or more amphiphilic stabilizers. Preferred amphiphilic stabilizers are nicotinic acid derivatives, particularly nicotinamide, and naturally-occurring $\alpha$ -amino acids having a lipophilic side chain, for example phenylalanine, proline, leucine and isoleucine.			

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### LIQUID IMMUNOGLOBULIN FORMULATIONS

This invention relates to stable preparations of immunoglobulins.

A number of processes are known for the production of immunoglobulin preparations, particularly intravenously injectable forms of IgG (iv-IgG) from fractions of human blood plasma. In order for the product to be intravenously injectable, it is necessary to remove or to avoid the formation of aggregates which have anticomplementary activity and which, if injected intravenously, can give rise to severe side reactions including anaphylactic shock. The majority of iv-IgG preparations available for clinical use are lyophilized (freeze-dried) for improved stability on storage, but such preparations must be reconstituted with diluent, e.g. sterile water or saline, before use. This reconstitution step is inconvenient and time-consuming, and opens up the possibility of contamination of the product. It is therefore desirable to produce pharmaceutical compositions of iv-IgG which are intended to be stored and used in liquid (aqueous solution) form and which have the necessary degree of stability for such storage. Such compositions are referred to hereinafter as liquid preparations of iv-IgG. Some such preparations are already commercially available.

Although IgG products for intravenous injection contain only very small amounts of aggregates (trimers or higher polymers of IgG molecules), they may contain quite large amounts of IgG dimers, as may be determined for example by high pressure liquid chromatography (HPLC). These dimers do not give rise to anaphylactic shock, and generally have not been regarded as a problem. Indeed in many product specifications, monomers and dimers are considered together under a heading such as "functional IgG".

It has been found by Tankersley et al (Molecular Immunology 25, 41-48 1988) that the dimer content of IgG preparations is higher the more donors contribute to the plasma pool from which the IgG was obtained. Thus dimer cannot be detected in IgG obtained from a single individual and is relatively low in hyperimmune IgG obtained from a few hundred to a few thousand donors who have been immunised against a specific disease antigen, whereas it reaches high levels in IgG prepared from donor pools of 10,000 or more donors. The authors conclude that the IgG dimers are idiotype-anti-idiotype dimers which are formed when an antibody from one donor recognises the antigen-binding region of an antibody from a different donor and binds to it. Dimers and monomers are present in equilibrium, and the dimer content increases with total immunoglobulin concentration.

The same authors found that dimer formation increases with storage time; the dimer content of a typical preparation may double during the first week of storage, and continue to rise slowly thereafter. When an IgG preparation is lyophilized shortly after it is produced, this increase in dimer formation is prevented from taking place. However if the preparation is intended to be stored and used in liquid form, the dimer concentration will increase on storage.

The same type of dimer formation may occur in immunoglobulins other than IgG, for example in IgA, IgD and IgE. Furthermore, dimer formation is also observed in preparations of monoclonal antibodies, although the mechanism of dimer formation in MAbs may differ from that proposed by Tankersley et al.

It has now been found by the present inventors that although IgG dimer, unlike higher polymers, does not cause anaphylactic shock, nevertheless IgG preparations with a high dimer content are less well tolerated on intravenous injection and can give rise to undesirable side effects including fever, nausea and sometimes lowered blood pressure. Hypotensive side effects have been detected in a rat model by Bleeker et al (Vox Sanguinis 52, 281-290, 1987), and this also shows an apparent correlation with the dimer content. It is therefore desirable to stabilize preparations of immunoglobulins, particularly liquid preparations of iv-IgG, against dimer formation.

A number of additives have been used to stabilize iv-IgG and to improve tolerance to it on iv injection. These include glycine; disaccharides, e.g. maltose and saccharose; sugar alcohols, e.g. sorbitol; polyethylene glycol; or small quantities of surfactants such as PEG-20-sorbitanmonooleate or PEG-10-nonyloxyphenol. However, it is found that none of these conventional stabilizers are effective in inhibiting dimer formation in liquid preparations of iv-IgG.

Since dimer content is a function of Ig concentration, it is of course possible to reduce dimer content by dilution of the liquid IgG preparations. This approach is not practical, however, as it would require the infusion of unacceptably high volumes of liquid into the patients.

According to the present invention, the problem is solved by the addition to the immunoglobulin formulation of an effective amount of an amphiphilic stabilizer.

Amphiphilic stabilizers used according to the invention are substances which contain within the molecule a strongly or moderately hydrophilic region as well as a strongly or moderately lipophilic region, but which are not tensides, that is, they do not form micelles in aqueous solution at the concentrations at which they are used, but remain in monomeric form. The amphiphilic stabilizers of the invention contain within the molecule one or more groups selected from carboxylic acid, sulphonic acid, phosphoric acid, (all in free acid or pharmacologically acceptable salt form), keto-, aldehyde, hydroxy-, amino- or amide groups; as well as one or more lipophilic groups containing from 3 to 12 carbon atoms, preferably from 4 to 10 carbon atoms, and optionally one atom of nitrogen or sulphur. These groups are preferably selected from straight or branched chain alkyl groups, straight or branched chain alkenyl groups, and aromatic, heteroaromatic, aliphatic or heteroaliphatic rings.

If a nitrogen atom is present in the lipophilic group, it is preferably in tertiary form, for example in a pyridine ring. Preferred non-cyclic lipophilic groups are branched-chain alkyl groups containing from 4 to 10, preferably 4 to 6 carbon atoms.

Clearly any compound used as stabilizer for iv-IgG must itself be pharmaceutically

acceptable for intravenous injection at the concentrations used. It is also preferred that it does not chemically change the IgG molecule, and that it has no significant buffer capacity at pH values between pH 4 and pH 8.

The preferred amphiphilic stabilizers are nicotinic acid and its derivatives, for example nicotinamide, nicotinamide N-oxide and N'-methyl nicotinamide, of which nicotinamide is particularly preferred.

A further preferred group of amphiphilic stabilizers is that of naturally-occurring  $\alpha$ -amino acids having uncharged lipophilic side-chains, as well as derivatives of such amino acids in which the carboxylic acid group is replaced by a group of formula  $-\text{CONH}_2$ ,  $-\text{CONHR}$ ,  $-\text{CH}_2\text{OH}$ , or  $-\text{COOR}$ , where R is  $\text{C}_{1-4}$ -alkyl. Such amino acids are phenylalanine, methionine, leucine, isoleucine, proline and valine, of which phenylalanine, proline, leucine and isoleucine; particularly proline, leucine and isoleucine; more particularly proline are preferred.

Japanese Patent Publication No 61-194035 discloses liquid gamma-globulin preparations which are subjected to heat treatment in the presence of a stabilizer which is a monosaccharide, disaccharide or sugar alcohol in the amount of 10 - 100 g / 100 ml and an auxiliary stabilizer which may be a neutral amino acid for example valine, leucine or isoleucine, or a salt of a carboxylic acid.

The present invention provides a liquid immunoglobulin preparation, particularly a liquid preparation of immunoglobulin G for intravenous injection, containing one or more amphiphilic stabilizers, as herein defined, in a total amount of at least 0.2 mmol per gram of immunoglobulin and at a total concentration of at least 20 mmol/litre, provided that, if the preparation contains 100 g/l or more of monosaccharide, disaccharide or sugar alcohol, then at least one amphiphilic stabilizer is other than a neutral amino acid or a salt of a carboxylic acid, and is preferably selected from nicotinic acid and its derivatives.

Preferred stabilizers are compositions comprising nicotinamide together with one or more of the above amphiphilic amino acids or their derivatives. More preferred stabilizer

compositions comprise nicotinamide and proline, optionally together with one or more additional amphiphilic amino acids. Especially preferred compositions are mixtures of (a) nicotinamide and proline; (b) nicotinamide, proline and isoleucine; and (c) nicotinamide, proline, isoleucine and leucine. Preferably in such compositions the mole ratio of nicotinamide to total amphiphilic amino acids lies between 1:1 and 1:4. The most preferred composition is a mixture of nicotinamide, proline and isoleucine, preferably in a mole ratio of 1 : (0.8 - 2.0) : (0.8 - 2.0).

The immunoglobulin stabilized according to the invention may be any preparation of IgA, IgD, IgE or IgG, whether polyclonal or monoclonal, and whether isolated from human or animal blood plasma or produced by other means, for example by hybridoma or recombinant DNA technology. Preferably it is a preparation of IgG from human blood plasma which has been treated so as to be intravenously injectable and which is intended to be stored and used in liquid form. More preferably it is a polyvalent, intact immunoglobulin which has not been cleaved (for example with high pepsin concentrations) and which retains the structural and functional integrity of the 7S-IgG antibodies, including an intact Fc region. Preferably it is one obtained from blood serum fractions by a modified alcohol cryoprecipitation including treatment with low concentrations of pepsin at pH 4.

The IgG content of the liquid formulation is preferably between 3% and 16%, more preferably between 6% and 12%. The pH of the solution is preferably from pH 4 to pH 8, more preferably from pH 5 to pH 6, particularly from pH 5.2 to pH 5.4. At such relatively acidic pH values, it is important that the solution have low buffer capacity, to prevent any significant lowering of the pH of the recipient's blood upon intravenous injection. The tonicity of the solution may be adjusted to physiological values by the addition of one or more non-buffering substances for example sodium chloride, glycine, sucrose, maltose and sorbitol. Such liquid formulations may be administered by intravenous infusion for example at a dosage of 0.2 - 1.0 g of IgG per kg of body weight per day.

The quantity of amphiphilic stabilizer present in the compositions according to the invention is preferably from 0.2 to 6 mmol per gram of IgG, more preferably 1 to 3 mmol/g IgG. The immunoglobulin preparations may also contain other proteins, for example albumin.

A liquid iv-IgG preparation according to the invention containing an amphiphilic stabilizer may be stored for up to 2 years at temperatures between 2°C and 25°C without the dimer content rising to unacceptable levels. Such formulations are well tolerated upon intravenous injection.

Solutions of iv-IgG which are intended to be lyophilized and sold in solid lyophilized form may also be stabilized by adding amphiphilic stabilizers according to the invention, so as to reduce dimer formation during the time between preparation and lyophilization.

The following examples illustrate the invention:

#### **A. Preparative procedure for liquid iv-IgG preparation**

Crude IgG paste obtained by alcohol fractionation of pooled human blood plasma is dissolved in sterile water at 4°C and filtered. The solution is acidified to pH 4 and incubated with a small quantity of pepsin at pH 4, 37°C, then neutralized. The product is then diafiltered to remove any remaining alcohol, then the pH is adjusted to pH 5.3 and the solution is concentrated by ultrafiltration to give a final protein concentration of between 6% and 15% w/v.

The product may also be prepared as described in Swiss Patent No. 684 164.

#### **B. Measurement of Dimer Content**

The product is analysed by HPLC on a Hewlett Packard HP 1090, using a TSK G3000SW-XL column of dimensions 7.8 x 300 mm with a mobile phase of 0.04 M phosphate buffer and 0.2 M sodium chloride at pH 7.0. The flow rate is 0.7 ml/min. A sample of 1.3 µl of a 150 mg/ml solution is used, and protein is detected by UV absorption at 280 nm. Peak areas corresponding to aggregate (typical retention time 8 - 9 min), dimer (9 - 10.5 min) and monomer (10.5 - 13.5 min) are measured automatically, and dimer content is given by



$$D\% = \frac{AD}{AA + AD + AM} \times 100$$

where AA, AD and AM are the areas of the aggregate, dimer and monomer peaks respectively.

### C. Stability Tests

Liquid iv-IgG preparations are stored at ambient temperature (20-25°C) in sealed containers for periods of 80-90 days, and the dimer content measured at the end of this period.

#### Example 1.

To 1 liter of the standard liquid preparation prepared as in A above and having a protein content of 15% and a pH of 5.3 is added 24.75g phenylalanine (150 mmol/L, 1 mmol/g protein).

Stability data for Example 1 and for additional Examples 2 - 16 according to the invention, together with comparative examples A - G containing no additives or containing glycine only, are shown in Tables 1 and 2 below. Table 3 below shows the results of testing four liquid preparations each containing 12% protein in the rat hypotensive model as described by Bleeker *et al* (Vox Sanguinis 52, 281-290, 1987) after room temperature storage. Preparations according to the invention (Examples 17 - 19) gave only a 5% - 18% drop in blood pressure whereas the unstabilized preparation gave a drop of nearly 50%.

Table 1: Dimer content after 80 days storage

Example	Additives	Concentration of additive (mmol/L)	Concentration of protein (% w/v)	Dimer Content
A	None	--	15	20.2%
1	Phenylalanine	150	15	14.7%
2	Phenylalaninamide	150	15	12.5%
3	Phenylalaninol (2-amino-3-phenyl-1-propanol)	150	15	13.1%
4	2- phenylethyl-amine	150	15	11.7%
B	None	--	12	17.7%
5	Nicotinamide	120	12	12.5%
6	Nicotinic acid	120	12	13.3%
7	Nicotinamide + Phenylalanine	120 120	12	10.3%

Table 2. Dimer content after 90 days storage

Example	Additives	Concentration of additive (mmol/L)	Concentration of protein (% w/v)	Dimer Content
C	none	--	15	18.0%
D	Glycine	300	15	17.4%
8	Glycine Phenylalanine	200 140	15	12.6%
9	Glycine Nicotinamide	200 150	15	10.7%
E	none	--	6	11.4%
F	Glycine	300	6	11.2%
10	Glycine Phenylalanine	300 60	6	9.3%
11	Glycine Nicotinamide	300 60	6	8.7%
12	Methionine Leucine	60 60	6	9.8%
G	none	--	12	17.5%
13	Proline Nicotinamide	200 100	12	10.6%
14	Proline Leucine Isoleucine Nicotinamide	100 60 60 100	12	10.0%
15	Proline Leucine Isoleucine Nicotinamide	120 80 80 80	12	10.1%
16	Proline Isoleucine Nicotinamide Glycine	100 120 100 40	12	(70 days only) 9.4%

Table 3: Dimer content and blood pressure drop in rat model

Example	Additives	Conc. (mmol/L)	Protein conc. (% w/v)	Dimer content (%)	Blood pressure drop (%)
G	None	--	12	16.0	49
17	Glycine Phenylalanine Nicotinamide	100 120 120	12	7.8	5
18	Proline Nicotinamide	200 100	12	8.4	18
19	Proline Leucine Isoleucine Nicotinamide	100 60 60 100	12	7.9	6

## Claims:

1. A liquid immunoglobulin preparation containing one or more non-tenside amphiphilic stabilizers characterized in that they contain within the molecule one or more groups selected from carboxylic acid, sulphonic acid, phosphoric acid, keto-, aldehyde, hydroxy-, amino- or amide groups; as well as one or more lipophilic groups containing from 3 to 12 carbon atoms and optionally one atom of nitrogen or sulphur, in a total amount of at least 0.2 mmol per gram of immunoglobulin and at a total concentration of at least 20 mmol/litre, provided that if the preparation contains 100 g/l or more of monosaccharide, disaccharide or sugar alcohol, then at least one amphiphilic stabilizer is other than a neutral amino acid or a salt of a carboxylic acid.
2. A preparation according to Claim 1 in which any nitrogen atom in the lipophilic group of any amphiphilic stabilizer is tertiary.
3. A preparation according to Claim 1 which is a liquid preparation of immunoglobulin G for intravenous injection.
4. A preparation according to any one of the preceding claims containing nicotinic acid or a nicotinic acid derivative as an amphiphilic stabilizer.
5. A preparation according to any one of the preceding claims in which at least one amphiphilic stabilizer is selected from phenylalanine, methionine, leucine, isoleucine, proline, valine, or a derivative of any of these in which the carboxylic acid group is replaced by a group of formula  $-\text{CONH}_2$ ,  $-\text{CONHR}$ ,  $-\text{CH}_2\text{OH}$ , or  $-\text{COOR}$ , where R is  $\text{C}_{1-4}$  alkyl.
6. A preparation according to Claim 5 in which at least one amphiphilic stabilizer is selected from proline, leucine and isoleucine
7. A preparation according to Claim 6 containing proline and nicotinamide.

8. A preparation according to Claim 7 containing nicotinamide, proline and isoleucine as the only amphiphilic stabilizers.
9. A liquid preparation according to any one of Claims 3 to 8 having a pH between pH 5 and pH 6.
10. A method for the stabilization of liquid preparations of iv-IgG against dimer formation upon storage at a temperature between 2°C and 25°C comprising the step of adding to the preparation at least 20 mmol/litre of one or more non-tenside amphiphilic stabilizers characterized in that they contain within the molecule one or more groups selected from carboxylic acid, sulphonic acid, keto-, aldehyde, hydroxy-, amino- or amide groups; as well as one or more lipophilic groups containing from 3 to 12 carbon atoms and optionally one atom of nitrogen or sulphur, in a total amount of at least 0.2 mmol per gram of immunoglobulin.
11. A method according to claim 10 in which the preparation is not subjected to any heat treatment step involving temperatures above 50° C.
12. A method for the preparation of a lyophilized preparation of iv-IgG having a low dimer content, comprising the step of lyophilization of a liquid preparation stabilized by the method of Claim 10 or Claim 11.

# INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/EP 95/03522

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K39/395 A61K47/18

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 025 275 (TEIJIN LTD ;CHEMO SERO THERAPEUT RES INST (JP)) 18 March 1981	1-3, 5, 6,
Y	see claims 1-14	9-12
	---	4, 7, 8
X	EP,A,0 187 712 (ORTHO DIAGNOSTIC SYSTEMS INC) 16 July 1986	1-3, 9-12
Y	see claims 1, 5, 14	4-8
	---	1-12
Y	EP,A,0 196 761 (GREEN CROSS CORP) 8 October 1986	1-12
Y	see page 3, line 21 - page 4, line 2 & JP,A,61 194 035 (GREEN CROSS CORP.) 28 August 1986	1-12
	cited in the application	
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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Intern. a: Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI  Section Ch, Week 8532  Derwent Publications Ltd., London, GB;  Class B04, AN 85-193554  &amp; JP,A,60 120 823 ( GREEN CROSS CORP ) , 28  June 1985  see abstract  ---</p>	1,10
Y	<p>DATABASE WPI  Section Ch, Week 9333  Derwent Publications Ltd., London, GB;  Class B04, AN 93-261569  &amp; JP,A,05 178 719 ( KANEBO LTD ) , 20 July  1993  see abstract  ---</p>	1-12
A	<p>EP,A,0 037 078 (GREEN CROSS CORP) 7  October 1981  see the whole document  ---</p>	1-12
A	<p>EP,A,0 392 717 (LILLY CO ELI) 17 October  1990  see the whole document  -----</p>	1-12



## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/EP 95/03522

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0025275	18-03-81	JP-A- 56025115	10-03-81
		JP-A- 56025116	10-03-81
		AT-T- 11370	15-02-85
		CA-A- 1165235	10-04-84
		US-A- 4362661	07-12-82
-----			
EP-A-0187712	16-07-86	US-A- 4597966	01-07-86
		AU-B- 590737	16-11-89
		AU-B- 5189286	17-07-86
		CA-A- 1285225	25-06-91
		JP-A- 61218528	29-09-86
-----			
EP-A-0196761	08-10-86	JP-A- 61191622	26-08-86
		CA-A- 1306691	25-08-92
		KR-B- 9403941	09-05-94
-----			
EP-A-0037078	07-10-81	JP-C- 1578821	13-09-90
		JP-A- 56135418	22-10-81
		JP-B- 62036493	07-08-87
		US-A- 4327086	27-04-82
-----			
EP-A-0392717	17-10-90	AU-B- 5252090	11-10-90
		CA-A- 2013600	04-10-90
		JP-A- 2290822	30-11-90